EXTRACTABLES AND LEACHABLES: DETERMINING RISK IN SINGLE-USE SYSTEMS FOR THE BIOLOGICS INDUSTRY

Single-use systems (SUS) are increasingly becoming the norm in biologics development and manufacturing. Around 85% of the pre-commercial biopharmaceutical sector uses SUS and it is increasingly being adopted for commercial manufacturing. SUS have significant advantages but are not without drawbacks. A 2018 survey showed that 73.3% of biologics insiders listed contamination from extractables and leachables to be a major problem.[1]

SINGLE-USE SYSTEMS

While a limited number of SUS products were traditionally used in biologics manufacturing, such as filter membranes and silicone tubing, a major shift took place in the 2000s with the introduction of several SUS products. Today, SUS are used for a variety of purposes, including filters, process containers (bags), tubing, connectors, gaskets, valves and packaging (finished products).

Growth in the SUS sector has been rapid, a trend that is predicted to continue. In 2013, SUS in the pharmaceutical industry was worth around USD 1.4 billion, by 2018 it had reached USD 3.5 billion, and it is estimated the sector will reach USD 11 billion by 2023.[2]

The majority of SUS are made from polymeric materials which are then sealed and sterilized. The primary benefit of this system to the biopharmaceutical industry is that the equipment is already sterile, thus removing the need for cleaning, sterilization and validation of the sterilization prior to usage. In effect, SUS is a more 'plug-and-play' approach to biologics production.

The undoubted benefits of SUS do not, however, diminish the potential drawbacks. These include the potential for breakage and the subsequent loss of production material, the high costs of disposal, and the potential for contamination through the migration of harmful substances into the drug product (DP).

SOURCES OF IMPURITIES IN SUS

Impurities can be added at any point in the supply chain, either intentionally or unintentionally. They may be present in the raw materials that constitute the SUS, result from the manufacturing processes that create the SUS, or form during the aging process of the materials in the SUS.

During biopharmaceutical production, impurities may also be introduced in several ways, including accumulation during manufacture, via interaction with the materials in the storage containers, from the environment, during materials processing, introduced with the excipient, or they may result from interaction with the material's surface.

Finally, they may also form once the DP has been manufactured and is in its container closure system. This could be through the aging process of the chemical materials, through the interaction between plastic and DP, or via a chemical reaction taking place in the material's polymeric structure.

A primary step for all biologics manufacturers is to ensure their suppliers adhere to a relevant pharmaceutical quality management system; they should consider the important quality attributes described in ICH Q10.

WHAT ARE EXTRACTABLES AND LEACHABLES (E&L)?

An extractable is a chemical entity, either organic or inorganic, that can extract substances from the components of a process system into a solvent under controlled conditions. These would normally be extreme conditions not encountered in the process – e.g. high heat, pressure, or multiple sterilization cycles. It can also mean strong acids or organic solvents.

The identification of extractables is important because it can lead to the identification of leachables. These are also chemical entities, either organic of inorganic, that can migrate from the components used in a process into the DP over the course of the system's life. Leachables can therefore end up in the DP, usually at a trace level in relation to the active pharmaceutical ingredient (API).

RISKS ASSOCIATED WITH LEACHABLES

Leachables present a problem to the quality of the DP as they may:

- Interact with either the API or excipient
- Compromise the product's stability, e.g. aggregation, increase in particulates
- Interfere with analytical methods or diagnostic tests
- Negatively impact process performance, e.g. cell growth, rate of drug release, drug solubility, pH, product yield, etc.

Impurities may also pose a toxicological risk if the leachable substance poses a health risk to the consumer. Finally, they may affect efficacy if the leachable interacts with the API or product formulation through chemical reaction, thereby altering its stability and potency.

To protect end users, regulators such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) require the identification and quantification of harmful leachable impurities that may migrate from the SUS. This must be achieved before the products are offered onto the market.

E&L STUDIES

Regulators require biopharmaceutical companies to undertake E&L studies. Extractables studies assess the performance of the material in the SUS, thereby determining what substances the patient may become exposed to during the taking of the medicine. Leachables studies are performed on the drug product, thereby identifying the substances to which patients may be exposed.

A variety of analytical techniques are used during E&L studies because no single analytical technique is available to detect all impurities. These can include Gas Chromatography Mass Spectrometry (GC-MS), 3D Gas Chromatography Mass Spectrometry (GC-QToF-MS), Liquid Chromatography Mass Spectrometry (LC-MS), pH, conductivity, Non-Volatile Residue (NVR) and Fourier Transform Infrared (FT-IR) spectroscopy, Total Organic Carbon (TOC), Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES) or ICP-MS, and Ion Chromatography (IC).

The principal E&L assessment steps are:

1. Profile extractables according to standard protocols, e.g. USP <665> and <1665> Polymeric Components and Systems Used in the Manufacturing of Drug Products
2. Recheck quality of extractable data, and supplement data when required
3. Perform risk analysis – identify critical SUS and determine risk controls
4. Determine toxicological limits for the critical target leachables based on:
   - Permitted daily exposure (PDE) values for identified substances
   - TTC/SCT (Threshold of Toxicological Concern/Safety Concern Threshold) for unidentified substances
5. Identify sampling points along the production process. Including the last filling step, these should represent the beginning, middle and end of the process
6. Semi-validate the analytical methods to be used on DP and demonstrate suitability of non-validated screening methods
7. Conduct quantitative and qualitative E&L correlation
8. Finalize risk assessment and, where necessary, enforce corrective and preventative actions

There are considerable challenges involved in the identification of leachables by mass spectrometry and sample preparation. For example, background compounds may yield ions that overlap with the leachables (spectral interference), which may prohibit the accurate quantification and identification of a leachable. An example of chemical interference might be the presence of matrix components that either suppress or enhance the detector response of the leachables through a chemical process. This would reduce the accuracy of the quantitative analysis and alter the spectrum quality.

To ensure a DP retains quality and is safe for the consumer, the manufacturer using the SUS must:

1. Distinguish between likely leachables - substances that are part of chemical construction of the material (extractables)
2. Filter extractables as probable leachables into relevant and non-relevant using simulation strategies
3. When required for complex drug formulations, use (semi-) validated target analysis (e.g. Validated Limit Test)
4. The toxicological calculated limit (AET (PDE)) should not to be equated with the analytical limit. It is important that analytical uncertainty is taken in account and specified accurately
5. If a substance is detected above the default AET (TTC/SCT) but cannot be identified, the TTC/SCT default must be assumed correct

As SUS become progressively prevalent in the biologics industry, and especially as they are introduced into downstream processing, so the question of safety becomes increasingly important. Manufacturers need to demonstrate to regulatory authorities and their own internal quality assurance systems, that the DP is unaffected by E&L and this means validation studies are required.

The issue is made more complex by the fact each manufacturer will rely upon a different process for each DP. Since these processes will also differ between manufacturers, it is clear to see why no single test, or set of tests, can effectively demonstrate to regulators that the DP is unaffected by E&L.

Without a clear specification or guidance document issued by an approval agency mandating testing protocols or setting levels for compliance, manufacturers are advised to partner with a contract research organization, such as SGS, with the breadth of experience to ensure accurate comprehensive testing of the relevant materials.

TO LEARN MORE ABOUT E&L STUDIES, CONTACT:

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